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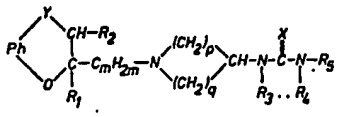
(54) N-Oxacyclic-alkylpiperidyl-diazacompounds, process for their manufacture and pharmaceutical compositions containing them

(57) The invention concerns compounds of the formula I



(I),

wherein Ph is unsubstituted 1,2-phenylene or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylene-dioxy, halogeno or trifluoromethyl, each of R_1 and R_2 is hydrogen or lower alkyl, each of R_3 and R_4 is hydrogen, lower alkyl or (R_3 + R_4) is Ph or lower alkylene separating both nitrogens by 2 to 4 carbon atoms, R_5 is hydrogen, lower alkyl or HPh, X is oxo, thioxo, imino or lower alkylimino, Y is epoxy, epithio or sulfinyl, m is an integer from 1 to 7, each of p and q is an integer from 1 to 3, but (p+q)=4, and acid additional salts thereof. The compounds exhibit stimulant and antidepressive effects. They are prepared by reduction of corresponding amides.

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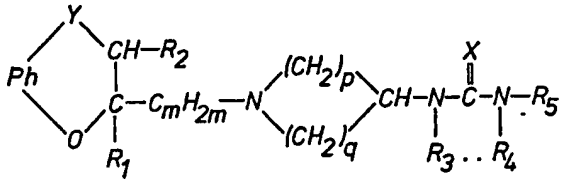
SPECIFICATION

N-Oxacyclic-alkylpiperidyl-diazacompounds, process for their manufacture and pharmaceutical compositions containing them

The present invention concerns the manufacture of new N-oxacyclic-alkylpiperidyl-diazacompounds of the general formula I



(I),

wherein Ph is unsubstituted 1,2-phenylene or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, halogeno or trifluoromethyl, each of R_1 and R_2 is hydrogen or lower alkyl, each of R_3 and R_4 is hydrogen, lower alkyl or (R_3 + R_4) is Ph or lower alkylene separating both nitrogens by 2 to 4 carbon atoms, R_5 is hydrogen, lower alkyl or HPh, X is oxo, thioxo, imino or lower alkylimino, Y is epoxy, epithio or sulfinyl, m is an integer from 1 to 7, each of p and q is an integer from 1 to 3, but (p+q) = 4, or of acid addition salts, especially of therapeutically acceptable acid addition salts thereof. The 1,2-phenylene group Ph is preferably unsubstituted or monosubstituted, and its up to three substituents are illustrated by the following groups: lower alkyl, e.g. methyl, ethyl, n- or i-propyl or -butyl; lower alkoxy, e.g. methoxy, ethoxy, n- or i-propoxy or -butoxy, lower alkylenedioxy, e.g. methylenedioxy, 1,1- or 1,2-ethylenedioxy, halogeno, e.g. fluoro, chloro or bromo or trifluoromethyl.

Each of R_1 to R_5 is preferably hydrogen, but also lower alkyl, advantageously methyl, or another of those mentioned above. The symbol R_5 may also be phenyl, unsubstituted or substituted as illustrated by H-Ph above. The symbols R_3 and R_4 taken together may also be Ph or lower alkylene separating both nitrogens by preferably 2 or 3 carbon atoms, e.g. 1,2-ethylene, 1,2- or 1,3-propylene, 1,2-, 1,3- or 2,3-butylene. The symbol X is preferably oxo, but also thioxo, imino or lower alkylimino and Y is preferably epoxy, but also epithio or sulfinyl. Of said integers m is preferably 1 to 4 and C_mH_{2m} advantageously represents methylene, 1,1- or 1,2-ethylene, 1,2- or 1,3-propylene, 1,2-, 1,3- or 1,4-butylene; and each p and q is preferably 2.

All of the basic compounds of the general formula I can be in the form of acid addition salts, especially therapeutically acceptable acid addition salts, e.g. derived from the acids listed below.

As used above and hereinafter in connection with organic radicals or compounds respectively, the term "lower" defines such with up to 7, preferably up to 4, and advantageously 1 or 2 carbon atoms.

The compounds of the invention exhibit valuable pharmacological properties, for example, stimulant and antidepressive effects. This can be demonstrated in animal tests, using advantageously mammals, such as rats or monkeys, as test objects. The compounds of the invention can be applied to the animals enterally, e.g. orally, or parenterally, e.g. subcutaneously, intraperitoneally or intravenously, for example in the form of aqueous solutions or starchy suspensions. The dosage may range between about 0.1 to 100 mg/kg/day, preferably between about 1 to 50 mg/kg/day, especially between about 5 and 25 mg/kg/day. Said stimulant and antidepressive effects can be observed, for example, in male albino rats, which are allowed unrestricted access to food and water, except during experimental sessions. Behavioral testing takes place in standard, sound-insulated conditioning chambers, which contain a response lever. Electrical shocks are delivered through the grid floor. The response lever is connected to solid-state programming equipment, which controls the delivery of the electrical shocks. The number of responses and number of shocks received are both recorded. Said rats are first trained to avoid the onset of electrical shock by pressing the lever. Thereafter, the programming equipment is adjusted so that each lever-press postpones the onset of shock for 30 seconds. If the animal fails to press the lever within this time interval, brief electrical shocks are delivered every 15 seconds until the animal again presses the lever. Prior to each test session the rats are placed in the chambers for a fifteen minute warm-up period, during which responding is not recorded. Immediately thereafter the test compounds are given either within saline, or a 3% colloidal corn starch suspension in 5% aqueous polyethyleneglycol 400, containing one drop of polyoxyethylene-20-sorbitan monooleate per 10 ml, administered either orally or intraperitoneally. Thus, for example, the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone, especially the levorotatory form thereof, e.g. the 1-(S)-hydrobromide or fumarate, illustrative of the compounds of formula I, when intraperitoneally applied at doses as low as 2.5 mg/kg/day, significantly increases the rat's avoidance responding, which compares favorably with 5 mg/kg/day i.p. of methylphenidate (a classical stimulant).

Said compound of the invention exhibits a unique mechanism of action; it is apparently not a biogenic amine uptake blocker, a mianserin-like presynaptic α-noradrenergic blocker, an amphetamine-like stimulant prone to abuse liability, not an anticholinergic nor antihistaminic, i.e. it is free from said common side-effects of known antidepressants.

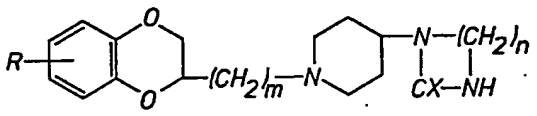
In another test male squirrel monkeys are trained to press a lever in such a Skinner box for avoiding an electric foot shock, applied through the floor grid. Each time a monkey presses the avoidance lever, the shock is postponed for 20 seconds; if it fails to press the lever within said period 0.5 second shocks are delivered at 20 second intervals until the monkey again presses the lever. Under control conditions the monkeys press the lever at a moderately steady rate and seldom receive more than 6 shocks during a four hour session. Measured are the avoidance responses and number of shocks received. Said hydrobromide or fumarate, when orally administered within 0.9% aqueous sodium chloride, positively changes both the avoidance response rate and number of shocks taken at doses as low as 2.5 mg/kg/day, as compared with a control session (on saline alone) preceding the drug session by one day.

Accordingly, the compounds of the invention are useful psychostimulants, for example in the treatment or management of depression or minimal brain dysfunction. Moreover, they are also valuable intermediates in the preparation of other useful products, especially of pharmacologically active compositions.

Particularly useful are compounds of the general formula I, wherein Ph is 1,2-phenylene unsubstituted or monosubstituted by lower alkyl, lower alkoxy, lower alkylenedioxy, halogeno or trifluoromethyl, each of R_1 and R_2 is hydrogen or lower alkyl, each of R_3 and R_4 is hydrogen, lower alkyl or (R_3 + R_4) is Ph or lower alkylene separating both nitrogens by 2 or 3 carbon atoms, R_5 is hydrogen, lower alkyl or HPh, X is oxo, thioxo, imino or lower alkylimino, Y is epoxy, epithio or sulfinyl, m is an integer from 1 to 4, each of p and q is an integer from 1 to 3, but (p + q).= 4; or therapeutically acceptable acid addition salt thereof.

Preferred compounds of the invention are those of the general formula I, wherein Ph is 1,2-phenylene unsubstituted or monosubstituted by alkyl or alkoxy, each with up to 4 carbon atoms, halogeno or trifluoromethyl, each of R_1, R_2, and R_5 is hydrogen or alkyl with up to 4 carbon atoms, each of R_3 and R_4 is hydrogen or (R_3 + R_4) represents alkylene with 2 to 4 carbon atoms separating both nitrogens by 2 or 3 carbon atoms, X is oxo, thioxo or imino, Y is epoxy or epithio, m is an integer from 1 to 4 and each of p and q is the integer 2, or a therapeutically acceptable acid addition salt thereof.

Outstanding are the compounds of the general formula II

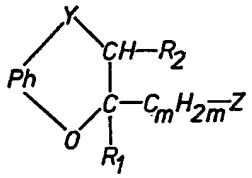


(II),

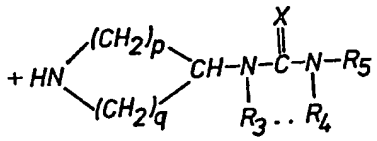
wherein R is hydrogen, alkyl or alkoxy each with up to 4 carbon atoms, halogeno or trifluoromethyl, m is an integer from 1 to 4, n is the integer 2 or 3 and X is oxo, thioxo or imino, or a therapeutically acceptable acid addition salt thereof.

The compound of this invention are prepared according to conventional methods, for example by

a) condensing a reactive ester of an oxacyclic alkanol of the general formula III with a 1-unsubstituted piperidyldiazacompound of the general formula IV



(III)



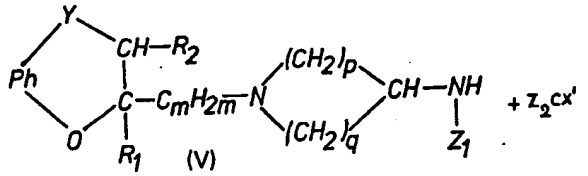
(IV)

wherein Z is a reactive esterified hydroxy group.

An esterified hydroxy group Z is, for example, such esterified by a strong inorganic or organic acid, above all a hydrohalic acid, e.g. hydrochloric, hydrobromic or hydriodic acid, sulfuric or an aromatic sulfonic acid, e.g. p-toluene or m-bromobenzene sulfonic acid. Said condensation is preferably carried out in the presence of a basic condensation agent, such as an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate, e.g. sodium, potassium or calcium hydroxide or carbonate, alkali metal hydrides, lower alkoxides or alkanoates, e.g. sodium hydride, methylate or acetate, as well as organic tertiary nitrogen bases, such as tri-lower alkylamines or pyridines, e.g. triethylamine or lutidine.

Another process for preparing the compounds of the invention consists in

b) reacting a compound of the general formula V with the carbonic acid derivative of the general formula VI



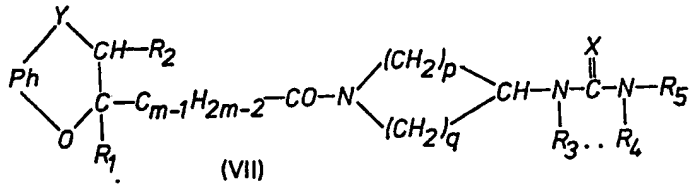
(V) (VI)

wherein Z_1 is R_3 or the grouping $R_3 \ldots R_4—NH—R_5$ and Z_2CX' is an ammonium or metal cyanate or thiocyanate, a lower alkyl isourea or thiourea, a cyanogen halide or amide, carbon disulfide or oxysulfide, a carbonic acid halide or 1,1-carbonyldiimidazole, provided that at least one of Z_1 and Z_2 contains nitrogen.

Said reaction provides either the addition of a carbamoyl group to the compound V, if Z_1 represents R_3, or the insertion of CX into V if Z_1 is the grouping $R_3 \ldots R_4—NH—R_5$. Said cyanate is preferably an alkali metal cyanate, a cyanogen halide advantageously the bromide and the carbonic acid halide preferably phosgene. Said reaction is carried out in the usual manner depending on Z_2. In case it is metallic, the reaction is performed in a neutral or acidic solvent or diluent, such as a water-miscible polar solvent, for example an aqueous lower alkanol, alkanone or saturated cyclic ether, e.g. ethanol, acetone, tetrahydrofuran or dioxan, or an alkylated formamide or sulfoxide, e.g. di-methylformamide or -sulfoxide. If Z_2 is non-metallic, a basic agent may be used as acid binder, such as an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate, e.g. sodium potassium or calcium hydroxide or carbonate; alkali metal hydrides, lower alkoxides or alkanoates, e.g. sodium hydride, methylate or acetate, as well as organic tertiary nitrogen bases, such as tri-lower alkylamines or pyridines, e.g. triethyl-amine or lutidine.

The compounds of the invention are also obtained by

c) reducing a compound of the general formula VII



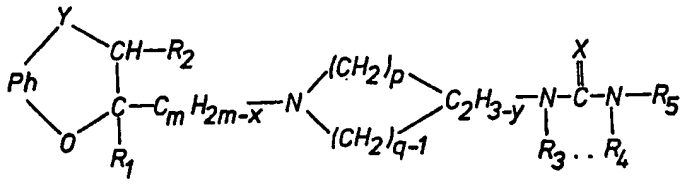
(VII)

wherein m is an integer from 1 to 7.

The reduction is carried out in the usual manner, preferably with the use of simple or complex light metal hydrides, such as diborane or alane, alkali metal boro- or aluminiumhydrides or -alkoxy-hydrides, e.g. lithium aluminiumhydride and/or sodium trimethoxy-borohydride.

Another process for preparing the compounds of the invention consists in

d) hydrogenating a compound of the general formula VIII



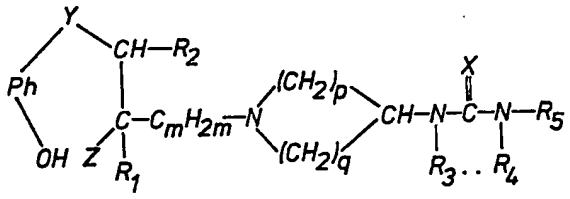
(VIII)

wherein each of x and y is the integer 0 or 2 and their sum x+y is 2 or 4.

The hydrogenation of said olefines VIII is performed in the usual manner, preferably with the use of catalytically activated or nascent hydrogen, such as hydrogen in the presence of cobalt, palladium, platinum or rhodium catalysts, e.g. cobalt sulfide or tris-(triphenylphosphine)-rhodium chloride (which are not poisoned by sulfur), or hydrogen generated electrolytically.

The compounds of the invention are also obtained by

e) ring-closing a reactive ester of a compound of the general formula IX



(IX)

wherein Z is a reactive esterified hydroxy group.

A reactive esterified hydroxy group is, for example, such esterified by a strong inorganic or organic acid, above all a hydrohalic acid, e.g. hydrochloric, hydrobromic or hydriodic acid, sulfuric or an aromatic sulfonic acid, e.g. p-toluene or m-bromobenzene sulfonic acid. Said ring-closure is preferably carried out in the presence of a basic condensation agent, such as an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate, e.g. sodium, potassium or calcium hydroxide or carbonate, alkali metal hydrides, lower alkoxides or alkanoates, e.g. sodium hydride, methylate or acetate, as well as organic tertiary nitrogen bases, such as tri-lower alkylamines or pyridines, e.g. triethylamine or lutidine.

The compounds of the invention so obtained can be converted into each other according to known methods. Thus, for example compounds with R_3 to R_5 being hydrogen, can be reacted with reactive esters of lower alkanols, e.g. such esterified by a strong inorganic or organic acid, above all a hydrohalic acid, e.g. hydrochloric, hydrobromic or hydriodic acid, sulfuric or an aromatic sulfonic acid, e.g. p-toluene or m-bromobenzene sulfonic acid, in order to obtain the corresponding N-substituted compounds. Depending on the molar amount of alkylating agent employed, the successive introduction of each R_3, R_4, and R_5 is accomplished. Compounds in which Y represents a sulfur atom can also be oxidized to the corresponding 4-oxides with the use of mild oxidants, such as periodates, e.g. sodium periodate in said polar solvents and at low temperatures, e.g. between about 0° and room temperature. Care should be taken in order to prevent overoxidation at overly long reaction times.

Finally, the compounds of the invention are either obtained in the free, basic form, or as a salt thereof. Any resulting base can be converted into a corresponding acid addition salt, preferably with the use of a therapeutically useful acid or anion exchange preparation, or resulting salts can be converted into the corresponding free bases, for example, with the use of a stronger base, such as a metal or ammonium hydroxide, basic salt or cation exchange, e.g. an alkali metal hydroxide or carbonate. Said acid addition salts are preferably such of therapeutically acceptable inorganic acids, for example hydrohalic, e.g. hydrochloric or hydrobromic acid; sulfuric, phosphoric, nitric or perchloric acid; or organic acids such as aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic; methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogen-benzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; or ascorbic acid. These or other salts, for example, the picrates, can also be used for purification of the bases obtained; the bases are converted into salts, the salts are separated and the bases are liberated from the salts.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The starting materials are known or if new, can be prepared according to known procedures, e.g. those illustrated in the examples herein.

Compounds of formula III can easily be obtained by reducing the corresponding 1,4-benzodioxan-2-yl-alkanoic acid to the corresponding alcohol with lithium aluminium hydride or sodium 2-methoxy-ethoxyaluminium hydride, and reactively esterifying it with a strong acid or its derivative mentioned above, e.g. a thionyl, phosphorus or benzenesulfonyl halide, in an organic solvent, such as benzene, preferably at a raised temperature.

Compounds of formula IV are obtained from corresponding 1-benzylpiperidones, which are converted into their O-alkyloximes or Schiff's bases of diaminoalkanes or -benzenes, which are reduced, either with the use of catalytically activated or nascent hydrogen, such as hydrogen in the presence of cobalt, palladium, platinum or rhodium catalysts, e.g. cobalt sulfide or tris-(triphenylphosphine)-rhodium chloride (which are not poisoned by sulfur), or hydrogen generated electrolytically, or with the use of simple or complex light metal hydrides, such as diborane or alane, alkali metal boro- or aluminium-hydrides or -alkoxyhydrides, e.g. lithium aluminiumhydride and/or sodium trimethoxyborohydride, to the mono- or diamines. These are further reacted with the carbonic acid derivative Z_2CX', e.g. an ammonium or metal cyanate or thiocyanate, a lower alkyl isourea or thiourea, a cyanogen halide or amide, carbon disulfide or oxysulfide, a carbonic acid halide or 1,1-carbonyldiimidazole, provided that at

least one of Z_1 and Z_2 contains nitrogen. Finally the benzyl moiety is hydrogenolytically removed in the end, preferably over palladium catalysts.

Compounds of formula V are similarly obtained by reacting the 3- or 4-piperidone with a reactive ester of the formula III, e.g. such in which the hydroxy group is esterified by a strong inorganic or organic acid, above all a hydrohalic acid, e.g. hydrochloric, hydrobromic or hydriodic acid, sulfuric or an aromatic sulfonic acid, e.g. p-toluene or p-bromobenzene sulfonic acid. The resulting products are converted into their O-alkyloximes or Schiff's bases of di-aminoalkanes or -benzenes, which are reduced either with the use of catalytically activated or nascent hydrogen to the mono- or diamines. The reduction is carried out as described for the starting materials of the formula IV. Compounds of formula V are also obtained from the previous esters of formula III by condensation with corresponding 3- or 4-benzylamino-piperidines and cleaving the benzyl group by hydrogenation.

Compounds VII are prepared from said 1,4-benzodioxan-2-yl-alkanoic acids by converting them into a halide, mixed anhydride or amide of imidazole, and reacting them with the corresponding piperidines.

The unsaturated compounds of formula VIII are preferably enamines prepared from the corresponding aldehydes and said piperidines, and the aldehydes are obtained by reduction of said acid halides according to Rosenmund, or of their nitriles with diisobutylaluminium hydride.

Finally the compounds of formula IX are prepared by the Mannich-reaction of said piperidines with corresponding aldehydes and/or ketones, brominating the resulting piperidinoalkanones, condensing the α-bromoketones obtained with mono-acetylcatechol, reducing the ketonic condensation product with sodium borohydride to the corresponding alcohol and reactively esterifying it as mentioned above.

In case mixtures of geometrical or optical isomers of the above compounds, e.g. I to IX, are obtained, these can be separated into the single isomers by methods in themselves known, e.g. by fractional distillation, crystallization and/or chromatography. Racemic products can likewise be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g. by the fractional crystallisation of d- or l-tartrates.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention further includes any variant of the present process, in which an intermediate product obtainable at any stage of the process is used as a starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

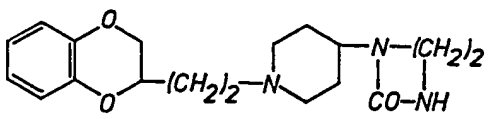
Mainly those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being especially valuable, e.g. those of formula II.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmacetical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral administration. Preferred are tablets and gelatin capsules comprising the active ingredient together with diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or glycine, and lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75%, preferably about 1 to 50% of the active ingredient.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade, and all parts wherever given are parts by weight. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mmHg.

EXAMPLE 1

The mixture of 4.9 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 2.54 g of 1-(4-piperidyl)-2-imidazolidinone, 5 g of anhydrous sodium carbonate and 100 ml of 4-methyl-2-pentanone is stirred and refluxed for 3 days. It is filtered, evaporated and the residue recrystallized from isopropanol, to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone of the formula



melting at 125°.

It is suspended in 10 ml of hot isopropanol, the suspension neutralized with 5N isopropanolic hydrogen bromide and the precipitate recrystallized from isopropanol, to yield the corresponding hydrobromide melting at 220—221° with decomposition.

The starting material is prepared as follows: The solution of 16 g of bromine in 10 ml of petroleum ether is slowly added to the solution of 6.7 g of allyl cyanide in 30 ml of the same solvent, while stirring and keeping the temperature at about −15°. After removal of the solvent the oily 3,4-dibromo-butyronitrile is obtained in quantitative yield.

227 g thereof are added dropwise in 5 equal parts to the stirred mixture of 85 g of catechol and 50 g of anhydrous potassium carbonate in 100 ml of refluxing acetone.

Another 50 g of potassium carbonate are added, followed by a slow addition of another part of nitrile. After 3 more cycles, using 40 g of potassium carbonate, one part nitrile each and sufficient acetone to allow stirring, the mixture is refluxed for 20 hours. It is filtered, the filtrate evaporated, the residue distilled and the fraction boiling at 105°/0.15 mm Hg collected, to yield the 1,4-benzodioxan-2-yl-acetonitrile.

The mixture of 111 g thereof, 63.5 ml of sulfuric acid, 160 ml of acetic acid and 160 ml of water is refluxed for 48 hours. It is poured on ice, the resulting solid collected and recrystallized from benzene-petroleum ether, to yield the 1,4-benzodioxan-2-yl-acetic acid melting at 100°.

The solution of 5.8 g thereof in 100 ml of benzene is added dropwise to 16.5 ml of a refluxing, 70% benzene solution of sodium bis (2-methoxyethoxy)-aluminium hydride under nitrogen. When addition is complete, the mixture is refluxed for 4 hours, cooled and poured slowly into 20 ml of 25% sulfuric acid. After filtration and removal of the solvent, the residue is taken up in methylene chloride, the solution washed several times with saturated aqueous sodium bicarbonate, dried and evaporated, to yield the oily 2-(2-hydroxyethyl)-1,4-benzodioxan.

The mixture of 3.6 g thereof, 5.7 g of p-toluenesulfonyl chloride and 20 ml of dry pyridine is stirred and cooled in an ice bath for 2 hours. Ice is then added to the mixture, the resulting solid is filtered off and recrystallized from ethyl acetate-petroleum ether, to yield the 2-(2-tosyloxyethyl)-1,4-benzodioxan melting at 82—3°.

To the solution of 1.6 g of 4-aminopyridine in 7 ml of dimethylformamide 2 g of 2-chloroethylisocyanate are added while stirring and keeping the temperature below 40°. After 2 hours 28 ml of water are added and stirring is continued for 2 hours at room temperature. The precipitate formed is filtered off, washed with water, dried and recrystallized from aqueous ethanol, to yield the 1-(4-pyridyl)-3-(2-chloroethyl)-urea melting at 120—122°.

To the suspension of 2.66 g thereof in 4 ml of boiling methanol, 2.68 g of 30.8% methanolic sodium methylate are added while stirring and the mixture is refluxed for 1 hour. It is filtered hot, washed with hot methanol, the filtrate evaporated and the residue is recrystallized from 90% aqueous ethanol, to yield the 1-(4-pyridyl)-2-imidazolidinone melting at 204—207°.

The solution of 5 g thereof in 45 ml of water is hydrogenated over 0.8 g of 10% ruthenium on carbon at 120° and 120 atm. until the hydrogen absorption ceases. It is filtered, the filtrate evaporated, the residue taken up in chloroform, the solution dried, evaporated and the residue recrystallized from methylene chloride-petroleum ether, to yield the 1-(4-piperidyl)-2-imidazolidinone melting at 155—157°.

EXAMPLE 2

The solution of 4 g of 1-[1-[2-(l-1,4-benzodioxan-2-yl)-acetyl]-4-piperidyl]-2-imidazolidinone in 50 ml of tetrahydrofuran is added to the cooled and stirred suspension of 1 g of lithium aluminium hydride in 100 ml of tetrahydrofuran at 25°. It is stirred at room temperature overnight and decomposed with 10 ml of ethyl acetate, 1 ml of water, 2 ml of 15% aqueous sodium hydroxide and 3 ml of water. The mixture is filtered, the filtrate evaporated and the residue dissolved in 25 ml of hot isopropanol. The solution is combined with that of 1.35 g of fumaric acid in 25 ml of hot isopropanol and the precipitate collected after cooling, to yield the l-1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone fumarate melting at 210—213°: $[\alpha]_D = -30.4°$ (methanol).

In the same manner the dextrorotatory salt is obtained, melting at 210—213°; $[\alpha]_D = +30.8°$ (methanol).

The starting material is prepared as follows: 19.4 g of 1,4-benzodioxan-2-yl-acetic acid and 12.1 g of *d*-α-methylbenzylamine are dissolvedin 100 ml of hot isopropanol. After standing overnight, the salt formed is filtered off and recrystallized five times from isopropanol. Experiments show that this is sufficient to optically resolve said acid. It is liberated with diluted hydrochloric acid, the mixture

extracted with diethyl ether and the extract evaporated, to yield the *d*-1,4-benzodioxan-2-yl-acetic acid with $[\alpha]_D = +49°$ (ethanol).

In like manner, using l-α-methylbenzylamine, the antipode acid is obtained, $[\alpha]_D = -49°$ (ethanol).

The solution of 3.4 g of said l-acid in 60 ml of tetrahydrofuran is stirred with 3.4 g of carbonyldiimidazole for 1 hour. Then 3.05 g of 1-(4-piperidyl)-2-imidazolidinone, suspended in 20 ml tetrahydrofuran are added and the mixture is stirred overnight. It is evaporated, the residue dissolved in ethyl acetate, the solution washed with N hydrochloric acid and 5% aqueous sodium hydroxide, dried and evaporated, to yield the 1-[1-[2-(l-1,4-benzodioxan-2-yl)-acetyl]-4-piperidyl]-2-imidazolidinone.

EXAMPLE 3

The mixtureof 3.34 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 1.83 g of 1-(4-piperidyl)-2-hexahydropyrimidinone, 4 g of sodium carbonate and 80 ml of 4-methyl-2-pentanone is refluxed for 3 days. It is filtered hot, the filtrate evaporated and the residue taken up in water. The suspension is made basic with ammonium hydroxide, extracted with chloroform, the extract dried and evaporated. The residue is dissolved in hot ethanol, the solution made acidic with 4.5N ethanolic hydrogen chloride, cooled and filtered, to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-hexahydropyrimidinone hydrochloride melting at 253—255°.

Analogously the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-benzimidazolidinone hydrochloride is obtained, melting at 185—189°.

The starting material is prepared as follows: To the ice cooled stirred solution of 62.5 ml of 1,3-diaminopropane in 100 ml of ethanol, 30 g of 1-benzyl-4-piperidone are added dropwise. The mixture is hydrogenated over 2 g of pre-reduced platinum oxide at 50° and 2.7 atm. for 9 hours. After theoretical hydrogen-uptake the catalyst is filtered off, the filtrate evaporated, the residue distilled and the fraction boiling at 145—160°/0.2 mmHg collected, to yield the 4-(3-aminopropylamino)-1-benzylpiperidine.

To the stirred, ice-cooled solution of 24.1 g thereof in 100 ml of tetrahydrofuran, 18.3 g of 1,1-carbonyldiimidazole in 250 ml of tetrahydrofuran are added dropwise. After stirring at room temperature for 18 hours the mixture is evaporated, the residue suspended in water, filtered off and recrystallized from ethanol, to yield the 1-(1-benzyl-4-piperidyl)-2-hexahydropyrimidinone melting at 178—180°.

The solution of 8 g thereof in 100 ml ethanol-acetic acid (1:1) is hydrogenated over 1.5 g 10% palladium on charcoal, at 50° and 2.7 atm. for 4 hours. After filtration through filter cell and removal of the solvent, the residue is taken up in water, the mixture made strongly alkaline with 50% aqueous sodium hydroxide, extracted with chloroform, the extract dried, filtered, evaporated and the residue recrystallized from ethanol, to yield the 1-(4-piperidyl)-2-hexahydropyrimidinone melting at 206—210°.

The 1-(4-piperidyl)-2-benzimidazolidinone is described in U.S.-patent No. 3,929,801.

EXAMPLE 4

To the stirred solution of 6 g of 1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(2-aminoethylamino)-piperidine in 10 ml of 50% aqueous ethanol, 1.4 ml of carbon disulfide are added dropwise at 25°. The mixture is refluxed for one hour, a drop of concentrated hydrochloric acid is added and refluxing is continued for 5 hours. After cooling overnight the mixture is filtered and the residue washed with ethanol, to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinthione hydrochloride melting at 292°.

The starting material is prepared as follows: The mixture of 10 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 10 g of 4-piperidone hydrochloride, 20 g of anhydrous sodium carbonate and 160 ml of dimethylformamide is stirred vigorously at room temperature for 48 hours. It is filtered, the residue washed with a small amount of dimethylformamide and the filtrate evaporated. The residue is dissolved in ethyl acetate, the solution extracted with hydrochloric acid, the extract made alkaline with 50% aqueous sodium hydroxide while cooling and re-extracted with methylene chloride. The latter extract is dried and evaporated, to yield the 2-[2-(4-oxopiperidino)-ethyl]-1,4-benzodioxan, which solidifies on standing.

To the solution of 18 g of thereof in 150 ml of ethanol, that of 23 ml of ethylenediamine in 30 ml of ethanol is added and the whole hydrogenated over 2 g of prereduced platinum oxide at 50° and 3 atm. until the requisite amount of hydrogen has been absorbed. The mixture is cooled, filtered and the filtrate evaporated, to yield the 1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(2-aminoethylamino)-piperidine as an oil.

EXAMPLE 5

According to the methods illustrated by the preceding examples, advantageously those indicated in the table below under "Ex.", the following compounds of Formula I are prepared from equivalent amounts of the corresponding starting materials:

$R_1 = R_2 = H$, $R_3 + R_4 = (CH_2)_2$, $X = O$ and $p = q = 2$, (2-position of Ph at Y)

No.	Ph	Y	m	R_5	Salt	Ex.	m.p. °C
1	1,2-phenylene	O	1	H	HCl	1	250–1
2	"	O	3	H	"	2	280–5
3	"	O	2	phenyl	"	1	263–5
4	4-CH_3–C_6H_3	O	2	H	"	1	245–6
5	5-CH_3–C_6H_3	O	2	H	"	1	218–0
6	6-CH_3O–C_6H_3	O	2	H	"	1	261–1
7	1,2-phenylene	S	2	H	–	2	95–9

The various starting materials can be prepared as follows:

The mixture of 10 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 2.4 g of sodium cyanide, 4 ml of water and 20 ml of ethanol is refluxed for 48 hours. It is evaporated, the residue taken up in water and extracted with diethyl ether. The extract is dried, evaporated and 5 g of the crude nitrile stirred and refluxed for 48 hours in a mixture of 2.8 ml of sulfuric acid, 7.2 ml of water and 7.2 ml of acetic acid. The mixture is poured into ice water, extracted with diethyl ether, the extract washed with water and re-extracted with aqueous sodium bicarbonate. The alkaline solution is made acidic with hydrochloric acid and extracted with diethyl ether. The extract is dried, evaporated, 2.5 g of the crude acid are dissolved in 25 ml of tetrahydrofuran and the solution treated with 3 g of carbonyldiimidazole for 30 minutes while stirring. 2.4 g of 1-(4-piperidyl)-2-imidazolidinone are added and the mixture is stirred overnight. It is evaporated, the residue dissolved in ethyl acetate, the solution washed with 5% aqueous sodium hydroxide and 5% hydrochloric acid, dried and evaporated, to yield the 1-[1-[3-(1,4-benzodioxan-2-yl)-propionyl]-4-piperidyl]-2-imidazolidinone.

To the solution of 12.6 g of N-phenylethylenediamine in 200 ml of methanol, 50 ml of 4.1 N ethanolic hydrogen chloride are added dropwise followed by 18.9 g of 1-benzyl-4-piperidone in 100 ml of methanol. Then, 9.45 g sodium cyanoborohydride are added in portions while stirring at room temperature. After 72 hours the mixture is filtered, the residue dissolved in water and the solution made basic with 12.5% aqueous sodium hydroxide. It is extracted with methylene chloride, the extract dried and evaporated to yield the 1-benzyl-4-(2-phenylaminoethylamino)-piperidine.

To the stirred solution of 14 g thereof in 100 ml of dry benzene, 170 ml of 12.5% phosgene in benzene are added dropwise at room temperature. After stirring overnight the gelatinous precipitate is filtered through a sintered glass funnel, the solid dissolved in hot water, the solution made basic with ammonium hydroxide and the precipitate filtered off, to yield the 1-(1-benzyl-4-piperidyl)-3-phenyl-2-imidazolidinone melting at 168—170°.

The solution of 10 g thereof in 200 ml ethanol-acetic acid (1:1) is hydrogenated over 1 g of 10% palladium on charcoal for 8 hours at 50° and 2.7 atm. After filtration through filter cell and removal of the solvent, the residue is made basic with 25% aqueous sodium hydroxide and the mixture extracted with diethyl ether. The organic layer is dried and evaporated, to yield the 1-(4-piperidyl)-3-phenyl-2-imidazolidinone.

The solution of 48.6 g of 2-(7-methyl-1,4-benzodioxan-2-yl)-acetic acid in the minimum amount of tetrahydrofuran is added dropwise at reflux rate to the stirred suspension of 13.4 g of lithium aluminium; hydride in 200 ml of dry tetrahydrofuran. The mixture is refluxed overnight, cooled, and decomposed by the addition of 13.4 ml of water, 13.4 ml 15% aqueous sodium hydroxide and 40 ml of water. It is filtered, evaporated, the residue distilled in a molecular still, and the fraction boiling at 155—165°/0.1 mmHg collected as colorless oil, to yield the 2-(2-hydroxyethyl)-7-methyl-1,4-benzodioxan.

To the refluxing solution of 75 g of 2-hydroxythiophenol in 660 ml of acetone is added 42 g of potassium carbonate, followed by the dropwise addition of the solution of 33.5 g of 3,4-dibromobutyronitrile in 50 ml of acetone while stirring. After 30 minutes refluxing, a second, third, and fourth addition of 42 g potassium carbonate and 33.5 g of 3,4-dibromobutyronitrile is made. The whole mixture is refluxed for 20 hours, cooled and filtered. The filtrate is evaporated and the residue distilled in a bulb to bulb apparatus at 185° and 0.5 mmHg, to yield the 2-(1,4-benzoxathian-2-yl)-acetonitrile.

The mixture of 57 g thereof, 85 ml water, 85 ml acetic acid and 32.6 ml of sulfuric acid is refluxed for 48 hours, cooled, poured onto ice and extracted with benzene. The organic phase is extracted with aqueous sodium bicarbonate, the aqueous phase acidified with hydrochloric acid and extracted with diethyl ether. The extract is dried and evaporated, to yield the corresponding carboxylic acid as an oil. Reacting it with carbonyldiimidazole and then with the 1-(4-piperidyl)-2-imidazolidinone as described in Example 2 gives the desired amide.

EXAMPLE 6

To the stirred solution of 6 g of 1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(2-aminoethylamino)-piperidine in 15 ml of tetrahydrofuran, that of 1.58 g of cyanogen bromide in 15 ml of tetrahydrofuran is added at 5°. After 2 hours the mixture is filtered, the residue dissolved in the minimum amount of water, the solution made strongly basic with sodium hydroxide and extracted with methylene chloride. The extract is dried, evaporated, the residue taken up in 50 ml of anhydrous ethanol and the solution combined with 0.1 g of sodium methoxide. It is refluxed overnight, evaporated, the residue taken up in water and the mixture extracted with methylene chloride. The extract is dried, evaporated, the residue dissolved in the minimum amount of isopropanol, the solution neutralized with ethereal oxalic acid and the solids collected to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imino-imidazolidine oxalate melting at 215—220° with decomposition.

EXAMPLE 7

Preparation of 10,000 tablets each containing 5 mg of the active ingredient:

Formula:

1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone	50 g
Lactose	1,157 g
Corn starch	75 g
Polyethylene glycol 6,000	75 g
Talcum powder	75 g
Magnesium stearate	18 g
Purified water	q.s.

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 40 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 150 ml of water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets using concave punches with 6.4 mm diameter, uppers bisected.

Preparation of 10,000 capsules each containing 2.5 mg of the active ingredient:

Formula:

1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone	25 g
Lactose	1,875 g
Talcum powder	100 g

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance is placed in a suitable mixer and mixed first with the talcum, then with the lactose until homogeneous. No. 3 capsules are filled with 200 mg each, using a filling machine.

Analogously tablets and hard gelatin capsules of the other compounds, described in the remaining examples, are prepared.

EXAMPLE 8

To the solution of 2 g of 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone in the minimum amount of ethanol, the saturated solution of 0.78 g of fumaric acid in boiling ethanol is added. The mixture is cooled to 0° and the precipitate collected, to yield the corresponding fumarate melting at 190°.

EXAMPLE 9

To the solution of 3.47 g of 1-[1-[2-(1,4-benzoxathian-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone (Example 5, No. 7) in 10 ml of dioxane and 10 ml of methanol, the solution of 2.8 g of sodium metaperiodate in 20 ml of water is added dropwise while stirring at room temperature. After 2 hours the mixture is evaporated, the residue taken up in water and the mixture extracted with methylene chloride. The extract is washed with saturated aqueous sodium chloride, dried, evaporated and the residue recrystallized from isopropanol, to yield the 1-[1-[2-(4-oxo-1,4-benzoxathian-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone; m.p. 145°.

EXAMPLE 10

The mixture of 0.5 g of 1-[1-[3-(1,4-benzodioxan-2-yl)-1-propenyl]-4-piperidyl]-2-imidazolidinone, 25 ml of ethanol acetic acid (1:1) and 0.1 g of 10% palladium on charcoal is hydrogenated at 2.7 atm. and room temperature until one mole equivalent of hydrogen has been absorbed. The catalyst is filtered off, the filtrate evaporated, the residue dissolved in 5 ml of water and the solution made basic with aqueous ammonia. The mixture is extracted with methylene chloride, the extract dried, evaporated and the residue taken up in the minimum amount of isopropanol. The solution is acidified with ethanolic hydrogen chloride and the precipitate collected, to yield the 1-[1-[3-(1,4-benzodioxan-2-yl)-propyl]-4-piperidyl]-2-imidazolidinone hydrochloride melting at 282—285° with decomposition; it is identical with that obtained according to Example 5, No. 2.

The starting material is prepared as follows:

The mixture of 10 g of 2-(1,4-benzodioxan-2-yl)-oxiran, 2 g of potassium cyanide, 2 g of ammonium chloride and 25 ml of dimethylformamide is stirred at room temperature for 3 days. The mixture is diluted with water and extracted with methylene chloride. The extract is evaporated and the residue dehydrated by refluxing in a mixture of 11 ml of acetic acid, 11 ml of water and 4 ml of sulfuric acid for 24 hours. The mixture is diluted with ice, extracted with diethyl ether and the extract evaporated to yield the 3-(1,4-benzodioxan-2-yl)-acrylic acid. The solution of 5 g thereof in 25 ml of tetrahydrofuran is treated with 5.5 g of carbonyldiimidazole and the mixture stirred for 30 minutes. Then the solution of 4.6 g of 1-(4-piperidyl)-2-imidazolidinone in 25 ml of isopropanol is added and the mixture allowed to stand overnight. It is evaporated, the residue taken up in ethyl acetate, the solution washed successively with water, diluted aqueous sodium hydroxide and water and evaporated. The residue is dissolved in 100 ml of tetrahydrofuran, cooled in an ice bath and treated dropwise with 20 ml of a 1.2 molar solution of alane triethylamine complex while stirring. After 5 hours, the cold mixture is treated dropwise with 10 ml of 25% aqueous sodium hydroxide, the organic solvent phase is decanted from the pasty slurry of inorganic salts and evaporated to give the 1-[1-[3-(1,4-benzodioxan-2-yl)-1-propenyl]-4-piperidyl]-2-imidazolidinone.

EXAMPLE 11

The mixture of 4 g of 2-(2-tosyloxyethyl)-6,7-dichloro-1,4-benzodioxan, 1.69 g of 1-(4-piperidyl)-2-imidazolidinone, 10 g of anhydrous sodium carbonate and 100 ml of 4-methyl-2-pentanone is stirred and refluxed for 2 days. It is filtered, evaporated and the residue recrystallized from acetone, to yield the 1-[1-[2-(6,7-dichloro-1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone melting at 165°.

It is suspended in 10 ml of hot ethanol, the suspension neutralized with 5N ethanolic hydrogen chloride and the precipitate recrystallized from ethanol-diethyl ether, to yield the corresponding hydrochloride melting at 250°.

The starting material is prepared as follows: To the solution of 60 g of catechol in 200 ml of diethyl ether is slowly added 93 g of sulfuryl chloride during 2 hours while stirring and keeping the temperature at about 0°. After standing for 2 days at room temperature, the mixture is evaporated and the residue recrystallized twice from benzene, to yield the 4,5-dichlorocatechol melting at 85—90°. To 53.4 g thereof are added dropwise 5 equal parts of 89 g of 3,4-dibromobutyronitrile, in the presence of 33 g of anhydrous potassium carbonate and 800 ml of acetone while refluxing and stirring. Another 20 g of potassium carbonate are added, followed by the slow addition of another part of nitrile. After 3 more cycles, using 20 g of potassium carbonate per part of nitrile each, and sufficient acetone to allow stirring, the mixture is refluxed for 20 hours. It is filtered, the filtrate evaporated, the residue taken up in methylene chloride, the solution washed with water, dried and evaporated. The residue is recrystallized from isopropanol with the aid of charcoal, to yield the 6,7-dichloro-1,4-benzodioxan-2-yl-acetonitrile melting at 110°.

The mixture of 59 g thereof, 24 ml of sulfuric acid, 60 ml of acetic acid and 60 ml of water is refluxed for 48 hours. It is poured on ice, the resulting solid collected and recrystallized from aqueous ethanol, to yield the 6,7-dichloro-1,4-benzodioxan-2-yl-acetic acid melting at 145—147°.

The solution of 2.63 g thereof in 40 ml of benzene-tetrahydrofuran (1:1) is added dropwise to 5.5 ml of a refluxing, 70% benzene solution of sodium bis (2-methoxyethoxy)-aluminium hydride under nitrogen. When the addition is complete, the mixture is refluxed for 2.5 hours, cooled and poured slowly into 6.7 ml of 20% sulfuric acid. After filtration and removal of the solvent, the residue is taken up in methylene chloride, the solution washed several times with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride, dried and evaporated, to yield the oily 2-(2-

hydroxyethyl)-6,7-dichloro-1,4-benzodioxan, boiling at 180—190°/0.1 mm Hg.

The mixture of 15.2 g thereof, 17.5 g of p-toluenesulfonyl chloride and 40 ml of dry pyridine is stirred and cooled in an ice bath for 2 hours. Ice is then added to the mixture, the resulting solid is filtered off and recrystallized from ethyl acetate, to yield the 2-(2-tosyloxyethyl)-6,7-dichloro-1,4-benzodioxan melting at 135—138°.

EXAMPLE 12

450 g of d-1-[1-[2-(l-1,4-benzodioxan-2-yl)-acetyl]-4-piperidyl]-2-imidazolidinone are added portionwise during 100 minutes to the stirred suspension of 100 g of lithium aluminiumhydride in 6,500 ml of tetrahydrofuran at 2—6°. The mixture is stirred at room temperature for 19 hours, cooled again and 100 ml of water are added during 100 minutes, at 8—12°, followed by 100 ml of 15% aqueous sodium hydroxide and 300 ml of water. The mixture is stirred for 30 minutes in the cold and 90 minutes at room temperature. It is filtered, the residue washed with 2,000 ml of tetrahydrofuran and the filtrate evaporated to yield the l-1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone melting at 119—122°; $[\alpha]_D^{25} = -47.3°$ (c = 1 in methanol).

1,191 g thereof are dissolved in 3,000 ml of 95% aqueous ethanol at 60°, 120 g of charcoal are added and the mixture is stirred for 5 minutes. It is filtered, the residue washed with 200 ml of 95% ethanol and the filtrate combined with the solution of 441 g of fumaric acid in 7,200 ml of 95% ethanol at 60°. The resulting suspension is diluted with 1,000 ml of 95% ethanol and stirred at room temperature for 3 hours. It is filtered, the residue washed with 500 ml of 95% ethanol and 800 ml of anhydrous diethyl ether, to yield the l-1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone fumarate melting at 216—217° with decomposition; $[\alpha]_D^{25} = -31.6°$; (c = 13.73 mg/ml, in water); it is identical with that obtained according to Example 2.

The starting material is prepared as follows: To the solution of 1,134 g of bromine in 1,400 ml of ethyl acetate 472 g of allyl cyanide are added dropwise while stirring for 90 minutes at −10°—0°. The resulting solution of 3,4-dibromobutyronitrile is added all at once to the solution prepared from 705 g of catechol and 1,987 g of anhydrous potassium carbonate in 5,000 ml of refluxing ethyl acetate, while stirring at 35° under nitrogen. The mixture is refluxed for 4 hours and stirred overnight at room temperature. It is filtered, the residue washed with 2,000 ml of ethyl acetate, the filtrate evaporated, the residue distilled and the fraction boiling at 138°/1.4—131°/1.1 mm Hg collected, to yield the 1,4-benzodioxan-2-yl-acetonitrile.

The solution of 1,647 g thereof in 2,760 ml of glacial acetic acid is added to the hot mixture of 858 ml of concentrated sulfuric acid and 2,670 ml of water and the whole is refluxed for 17 hours. It is poured into 8,200 ml of cold water, stirred for 3 hours, filtered and washed with 9,000 ml of water to yield the 1,4-benzodioxan-2-yl-acetic acid melting at 87—90°.

To the mixture of 3,374 g thereof and 3,500 ml of anhydrous ethanol the solution of 2,105 g of l-α-methylbenzylamine in 500 ml anhydrous ethanol is added and the mixture is stirred for 3 hours at room temperature. After standing at 4—5° for 2 days the salt formed is filtered off and washed with 400 ml of ethanol, 400 ml of diethyl ether and 1,200 ml of isopropanol. 2,070 g of the residue are recrystallized from 2,000 ml of ethanol and washed with 500 ml of ethanol and diethyl ether each, to yield the l-1,4-benzodioxan-2-yl-acetic acid l-α-methylbenzylammonium salt melting at 132—133°.

1,827 g thereof are added to 10,000 ml of 1N hydrochloric acid while stirring for 20 minutes, 6,000 ml of diethyl ether are added and stirring is continued for 20 minutes. The aqueous layer is separated, extracted with 3,000 ml of diethyl ether, the combined ethereal solutions washed with 1,000 ml of water, dried and evaporated, to yield the l-1,4-benzodioxan-2-yl-acetic acid melting at 83—85°; $[\alpha]_D^{25} = -55, 42°$. (c = 12.325 mg/ml, in methanol).

The mixture of 400 g thereof, 2,000 ml of toluene and 320 ml of thionyl chloride is stirred at 80° for 3 hours and evaporated. The residue is taken up on 500 ml of chloroform and the solution again evaporated, to yield the l-1,4-benzodioxan-2-yl-acetyl chloride melting at 60—62°.

The solution of 434 g thereof in 1,000 ml of chloroform is added during 2 hours to the mixture of 400 g of 1-(4-piperidyl)-2-imidazolidinone, 4,000 ml of chloroform and 2,600 ml of 1N aqueous sodium carbonate, while stirring at 20—23°. After 2 hours the organic solution is separated, the aqueous phase extreacted with 1,000 ml of chloroform, the combined organic solutions washed with 1,000 ml of water, dried and evaporated. The residue is triturated with 1,000 ml of anhydrous diethyl ether,filtered and the residue washed with another 1,000 ml of diethyl ether, to yield the d-1-[1-[2-(l-1,4-benzodioxan-2-yl)-acetyl]-4-piperidyl]-2-imidazolidinone melting at 161—163°; $[\alpha]_D^{25} = +5.9°$ (c = 1, in chloroform).

EXAMPLE 13

To the stirred solution of 2 g of 1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(2-aminoethylamino)-piperidine in 25 ml isopropanol is added 1.65 ml of 4 N-hydrogenchloride in ethanol followed by 0.45 g of ammonium cyanate. After refluxing overnight, the reaction mixture is evaporated and heated in an oil bath at 130°C for 4 hours. The residue is dissolved in 100 ml of methylene chloride, washed with water, dried over anhydrous sodium sulfate and evaporated. The residue is taken up in 20 ml of hot isopropanol and 0.77 g of fumaric acid is added with stirring to effect solution. On cooling, the fumarate

of the desired 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone is obtained, m.p. 190°.

EXAMPLE 14

A mixture of 10 g of 1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(2-aminoethylamino)-piperidine and 8 g of carbonyl diimidazole in 100 ml of tetrahydrofuran is refluxed over night. The reaction mixture is evaporated, the residue taken up in 150 ml of methylene chloride and extracted three times with 50 ml of water. The methylene chloride is dried over anhydrous sodium sulfate and evaporated. The residue is dissolved in 50 ml of hot isopropanol and 3.8 g fumaric acid added with stirring. On cooling the fumaric acid salt of the desired 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone crystallizes out, m.p. 190°.

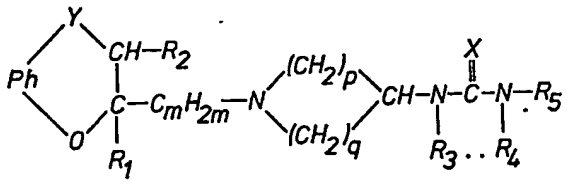
EXAMPLE 15

The mixture of 10 g of 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(1,2,5,6-tetrahydropyridyl)]-2-imidazolidinone, 100 ml of acetic acid, 50 ml of water and one gram of platinum oxide is hydrogenated at 3.4 atm. and 60° until one molar equivalent is absorbed. The reaction mixture is cooled to room temperature, the catalyst filtered off and the filtrate evaporated. To the residue is added 100 ml of water, excess of 3 N-sodium hydroxide (to pH 10) and 100 ml of methylene chloride. The methylene chloride extract is washed with water, dried over anhydrous sodium sulfate and evaporated. The residue is taken up in 50 ml hot isopropanol, treated with 3.8 g fumaric acid with stirring until solution occurs. On cooling, the fumaric acid salt of the desired 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone crystallizes. It melts at 190°.

The starting material is prepared as follows: The solution of 10 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 4.9 g of 1-(4-pyridyl)-2-imidazolidinone and 0.3 g potassium iodide is heated at 90° overnight. The reaction mixture is evaporated. The residue is dissolved in 500 ml of ethanol and with cooling and stirring treated with 30 g sodium borohydride, added in portions over two hours. The reaction mixture is evaporated to a small volume, diluted with 100 ml of water and extracted with 200 ml of methylene chloride. The methylene chloride solution is washed with water, dried over anhydrous sodium sulfate and evaporated to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-(1,2,5,6-tetrahydropyridyl)]-2-imidazolidinon, which is used as starting material.

CLAIMS

1. A compound of the general formula I



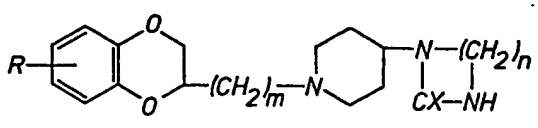
(I),

wherein Ph is unsubstituted 1,2-phenylene or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, halogeno or trifluoromethyl, each of R_1 and R_2 is hydrogen or lower alkyl, each of R_3 and R_4 is hydrogen, lower alkyl or ($R_3 + R_4$) is Ph or lower alkylene separating both nitrogens by 2 to 4 carbon atoms, R_5 is hydrogen, lower alkyl or HPh, X is oxo, thioxo, imino or lower alkylimino, Y is epoxy, epithio or sulfinyl, m is an integer from 1 to 7, each of p and q is an integer from 1 to 3, but $(p + q) = 4$.

2. A compound of the general formula I shown in claim 1, in which formula Ph is 1,2-phenylene unsubstituted or mono-substituted by lower alkyl, lower alkoxy, lower alkylenedioxy, halogeno or trifluoromethyl, each of R_1 and R_2 is hydrogen or lower alkyl, each of R_3 and R_4 is hydrogen, lower alkyl or ($R_3 + R_4$) is Ph or lower alkylene separating both nitrogens by 2 or 3 carbon atoms, R_5 is hydrogen, lower alkyl or HPh, X is oxo, thioxo, imino or lower alkylimino, Y is epoxy, epithio or sulfinyl, m is an integer from 1 to 4, each of p and q is an integer from 1 to 3, but $(p + q) = 4$.

3. A compound of the general formula I shown in claim 1 in which formula Ph is 1,2-phenylene unsubstituted or mono-substituted by alkyl or alkoxy each with up to 4 carbon atoms, halogeno or trifluoromethyl, each of R_1, R_2 and R_5 is hydrogen or alkyl with up to 4 carbon atoms, each of R_3 and R_4 is hydrogen or ($R_3 + R_4$) represents alkylene with 2 to 4 carbon atoms separating both nitrogens by 2 or 3 carbon atoms, X is oxo, thioxo or imino, Y is epoxy or epithio, m is an integer from 1 to 4, and each of p and q is the integer 2.

4. A compound of the general formula II



(II),

wherein R is hydrogen, alkyl or alkoxy each with up to 4 carbon atoms, halogeno or trifluoromethyl, m is an integer from 1 to 4, n is the integer 2 or 3 and X is oxo, thioxo or imino.

5. A free compound enumerated in Example 5.

6. 1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone and its l- and d-antipodes.

7. 1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-hexahydropyrimidinone.

8. 1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-benzimidazolidinone.

9. 1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinthione.

10. 1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imino-imidazolidine.

11. 1-[1-[2-(4-Oxo-1,4-benzoxathian-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone.

12. 1-[1-[2-(6,7-Dichloro-1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone.

13. A compound as claimed in any one of claims 1 to 12 in the form of an acid addition salt.

14. A compound as claimed in any one of claims 1 to 12, in the form of a therapeutically acceptable acid addition salt.

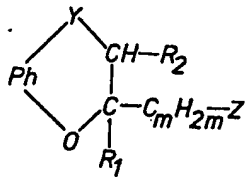
15. A compound of formula I substantially as described with reference to any of Examples 1 to 6 and 8 to 15.

16. A pharmaceutical preparation comprising a compound claimed in any one of claims 1 to 12, 14 and 15 in admixture or conjunction with a pharmaceutically suitable carrier.

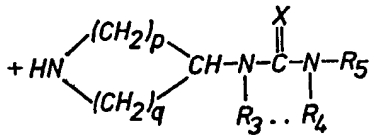
17. A pharmaceutical preparation as claimed in claim 16 substantially as described with reference to Example 7.

18. Process for the manufacture of a compound of the formula I shown in claim 1, in which formula all the symbols have the meanings given in claim 1, and of acid addition salts thereof, which consists in

a) condensing a reactive ester of the general formula III with a 1-unsubstituted piperidyl-diaza compound of the general formula IV



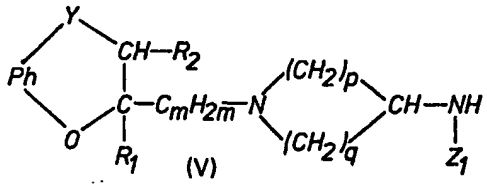
(III)



(IV)

wherein Z represents a reactive esterified hydroxy group or

b) reacting a compound of the general formula V with the carbonic acid derivative of the general formula VI

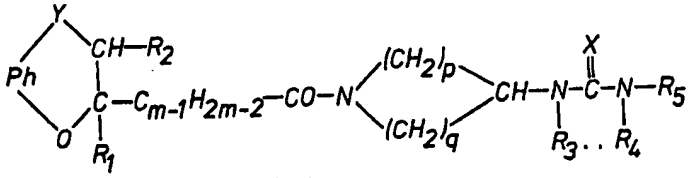


(V)

(VI)

wherein Z_1 is R_3 or the grouping $R_3 \ldots . R_4—NH—R_5$ and Z_2CX' is an ammonium or metal cyanate or thiocyanate, a lower alkyl isourea or thiourea, a cyanogen halide or amide, carbon disulfide or oxysulfide, a carbonic acid halide or 1,1-carbonyldiimidazole, provided that at least one of Z_1 and Z_2 contains nitrogen, or

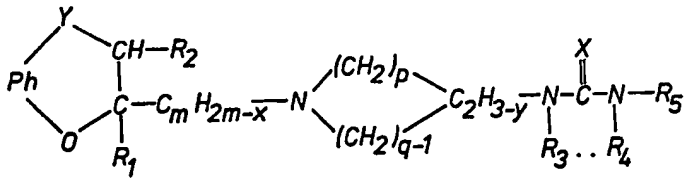
c) reducing a compound of the general formula VII



(VII)

wherein m is an integer from 1 to 7, or

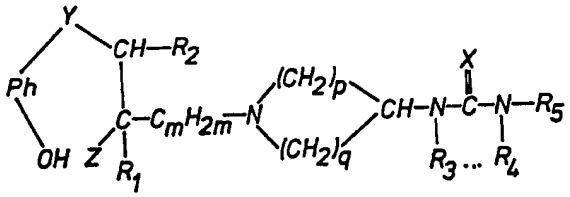
d) hydrogenating a compound of the general formula VIII



(VIII)

wherein each of x and y is the integer 0 or 2 and their sum x + y is 2 or 4, or

e) ring-closing a reactive ester of a compound of the general formula IX



(IX)

wherein Z is a reactive esterified hydroxy group, and, if desired, converting any resulting compound of formula I into another compound of the invention, and/or, if desired, converting a resulting free compound into an acid addition salt or a resulting acid addition salt into free compound or into another acid addition salt, and/or, if desired, resolving a mixture of isomers or racemats obtained into the single isomers or racemates, and/or if desired, resolving a racemate obtained into the optical antipodes.

19. The process for the preparation of end products of the general formula I, substantially as described in any one of Examples 1 to 6 and 8 to 11.

20. The process for the preparation of end products of the general formula I, substantially as described in any one of Examples 12 to 15.

21. The compounds of formula I when prepared according to either of claims 18 and 19.

22. The compounds of formula I when prepared according to claim 20.

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